

Remarks

The Applicants note the objection to Claim 15 under 35 U.S.C. §1.75(c). The Applicants have examined Claim 15 and do not see any objectionable subject matter or any objectionable form. However, in an effort to address whatever concern the Examiner may have, the Applicants have amended Claim 15 to depend solely from Claim 11. The Applicants have nonetheless added new Claims 20-22. They are exactly the same as Claim 15 except that they depend from Claims 12, 13, and 14, respectively. Withdrawal of the objection to Claim 15 is respectfully requested. Also, entry of Claims 20-22 into the official file and consideration on the merits is respectfully requested.

The Applicants note the rejection of Claims 11-12 and 14-19 under 35 U.S.C. §103 over the hypothetical combination of Rudd with Portoghese. The Applicants note with appreciation the Examiner's helpful comments theoretically applying those publications to the rejected claims. Nonetheless, the Applicants respectfully submit that one skilled in the art would not make the hypothetical combination and, in any event, any such hypothetical combination would still fail to teach or suggest the subject matter in the rejected claims.

The Applicants agree that Portoghese discloses compounds that are related to the compounds in the solicited claims. However, that disclosure is quite limited and it only discloses basically the notion of treating selected side effects such as tolerance and dependence caused by an opioid agonist which contains morphine or similar substances. This is disclosed in Column 2 at Lines 6-35 of Portoghese. Additionally, although there is no example in Portoghese, there is a suggestion about the inhibiting effect on respiratory depression. This can be seen in Column 3 at Lines 52-55. However, with respect to side effects limited to nausea and emesis to be treated as claimed by the Applicants, Portoghese discloses nothing about such treating effects.

The rejection helpfully mentions a portion of the text of Portoghese at Column 1, Lines 40-43

which states:

“...if a ligand acts as a single opioid receptor type or sub-type, the potential side effects mediated through other opioid receptor types can potentially be minimized or eliminated.”

The Applicants respectfully submit that this portion of Portuguese only indicates the generality that an opioid ligand “itself” which bonds to one type (for example, μ ,) can be those having no side effects caused by other types of opioid receptors (for example, δ or κ). Thus, the Applicants respectfully submit that the description noted above provides no teachings or suggestions concerning the claimed treating effects of nausea and emesis.

As a consequence of this deficiency, the rejection looks to Rudd to provide teachings for the inhibition of the emetic reflex. The rejection states that Rudd teaches naltrindole to inhibit the emetic reflex and refers specifically to the Rudd abstract and to Page 82 at Section 4.3, first paragraph.

Having carefully examined those portions of the Rudd disclosure, as well as the remainder of Rudd, the Applicants believe that there may be some confusion as to the Rudd disclosure. In that regard, the Applicants note that although Rudd discloses a discussion of naltrexone and naloxone, both of which have structures that are different from the compound set forth in the solicited claims, Rudd discloses nothing of value concerning naltrindole.

Another apparent area of confusion with respect to Rudd is that it only analyzes the mechanism of the emesis preventing effect by fentanyl against emesis caused by nicotine. Rudd discloses that naltrexone and naloxone, which are opioid antagonists, prevented anti-emetic actions of fentanyl and the doses of naloxone and naltrexone that prevented the anti-emetic actions of fentanyl had no effect on inducing emesis as set forth in §4.3, first paragraph of Rudd. In view of this fact, it becomes apparent that Rudd does not teach or suggest anything about the treating effects

of the compound in the solicited claims.

In other words, the Applicants respectfully submit that Rudd fails to teach or suggest that naltrindole inhibits the emetic reflex as recited in the rejection. In fact, the Applicants respectfully submit that Rudd teaches something quite different. In that regard, the Applicants agree that the Abstract of Rudd mentions naltrindole. That mention is in a sentence that states that the anti-emetic action of fentanyl was antagonized by naltrexone, naloxone, M8008 and MR2266. However, that sentence also states that the anti-emetic action of fentanyl was not antagonized by naloxone methyl bromide, naloxone methyl iodide, naltrindole, DIPPA and naloxonazine.

Naltrindole is also mentioned on Page 78 in Section 2.3 wherein naltrindole, among other things, was used as a test to determine the anti-emetic effect of fentanyl on emesis induced by nicotine. This can be seen in Table 2 where naltrindole is mentioned twice, once in combination with nicotine and once in combination with nicotine and fentanyl.

The next mention of naltrindole is on Page 80 in the right hand column. The data is provided in Table 2.

The Applicants respectfully submit that the critical mention of naltrindole is provided on Page 81 of Rudd in Section 4.1. That sentence is reproduced below for the Examiner's convenience:

We have used a number of selective opioid receptor antagonists to identify the receptors involved in the anti-emetic action of fentanyl in *S. murinus*. The δ/μ receptor antagonist M8008 (Sitsapesan and Parratt, 1989; McIntosh et al., 1992) but not the δ -opioid receptor antagonist naltrindole (Portoghese et al., 1988) or the irreversible selective κ -opioid receptor antagonist DIPPA (Schwartz et al., 1997), was capable of reversing the anti-emetic action.

The important point to take away from this portion of the Rudd disclosure is that naltrindole had no effect on the anti-emetic action of fentanyl against the emetic effect of nicotine. In other words, administering naltrindole made no difference at all. There was no effect. The Applicants

respectfully submit that these are the critical teachings to those skilled in the art.

This is in sharp contrast to the specific text mentioned in the rejection as being the critical portion of the teachings. The portion helpfully highlighted by the Examiner reads as follows:

It is perhaps worthy of consideration that the doses of naloxone, naltrexone, and M8008 that prevented the anti-emetic actions of fentanyl had no effect in their own right to induce emesis.

The Applicants note the important fact that naltrindole is not even mentioned in this location. Therefore, as noted above, the Applicants respectfully submit that Rudd provides no teachings or suggestions with respect to the actual treating effects of naltrindole.

However, this is sharply contrasted to the earlier teachings of Rudd on Page 80, wherein they state that administration of naltrindole had no effect at all on the anti-emetic action of fentanyl. What does this mean to one skilled in the art? The Applicants respectfully submit that those teachings provide no incentive for one skilled in the art to attempt to treat nausea and vomiting in accordance with the solicited claims with naltrindole. The reason for this is that one skilled in the art would have no reasonable expectation of success, which is an essential requirement in determining obviousness. One skilled in the art would have no reasonable expectation of success that naltrindole would effectively treat nausea and vomiting because Rudd specifically states that naltrindole had no effect on the anti-emetic action brought about by fentanyl.

In any event, since this is the only teaching presented by Rudd with respect to naltrindole, it is easily seen that there is no teaching or suggestion that administration of naltrindole alone would have any effect on nausea and/or vomiting as recited in the solicited claims. The Applicants therefore respectfully submit that one skilled in the art would have no incentive to hypothetically combine Rudd with Portuguese. Also, in view of the failure of Rudd to provide teachings or suggestions that naltrindole would or could have an effect on nausea and vomiting, hypothetically

non-disclosure with Portoghesse would result in the combined disclosure still failing to teach or suggest treating nausea and vomiting as recited in the solicited claims. Withdrawal of the rejection based on the hypothetical combinations therefore are respectfully requested.

In light of the foregoing, the Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,



T. Daniel Christenbury
Reg. No. 31,750
Attorney for Applicants

TDC/as
(215) 656-3381